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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,380	06/17/2005	Minoru Yoshida	18115-002US1	5153

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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
03/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,380	YOSHIDA ET AL.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/01/2007 08/03/2006 09/09/2005 07/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I, Claims 1-8, in the reply filed on 12/27/2007 is acknowledged. With respect to the requirement for an election of species, Applicants elected the species of compound SCOP 401, shown in FIG. 4 of the present application. In Formula 1 for SCOP 401, R11 is a hydrogen atom; R21 is a hydrogen atom; R22 is a hydrogen atom; R23 is a p-methoxybenzyl; R31 is a hydrogen atom; R32 is a hydrogen atom; R33 is sec-butyl; R41 and R42 are a cyclic structure by binding through a linear alkylene group with a three-carbon main chain; R43 is a hydrogen atom; X is pyridine-2ylthio, and n is 5. The elected species is readable on Claims 1-8.

Claim 9 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

Applicants' elected species has been found free of the prior art. The Examiner has moved onto the next species to which a 102(b) art rejection has been made.

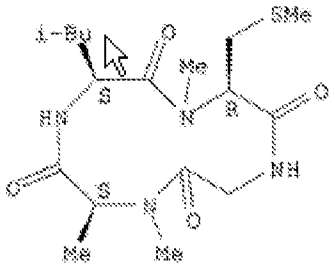
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Rich DH, "Synthesis of dehydro amino acids and peptides by dehydrosulfenylation. Rate enhancement using sulfenic acid trapping agents," J Org Chem. 1977 Nov 25;42(24):3815-20, made of record in the Lack of Unity mailed 9/27/2007.

Rich et al discloses the following peptide:



corresponding to Table II where the compound Cyclo[N-methyl-3-(methylsulfinyl)-L-ananylglycyl-N-methyl- L-alanyl-L-leucyl], also shown in the HCAPLUS search result, answer 15 of 17. In the instant case, X is unsbistitued alkyl (CH_3), R_{11} is alky (CH_3), R_{42} and R_{43} are acyclic structures (i-Bu and H), R_{41} is H, R_{32} and R_33 are acyclic structures (methyl and H), R_{31} is Methyl, R_22 and R_{23} are H, and R_{21} is H. The Compounds of Rich et al are members of antibiotic and phytotoxic compounds are intended for administration, thereby readable upon a pharmaceutical composition of claims 7 and 8, see column 1 and first paragraph on page 3815. Therefore, the invention as claimed is anticipated by the prior art. It is noted that claims 2-6 have been rejected because these claims do not provide any structural limitations for the particular inhibitor or agent claimed. Since the prior art disclose the same agent, as described above, all of the structural limitations have been met and therefore the reference anticipates the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the

conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated:
"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention.

In the instant case, the claims are drawn to compounds of forula I which are known to be histone deacetylase inhibitors in vitro.

(1) Level of skill and knowledge in the art:

The level of skill to practice the art of the instantly claimed invention is high with regard to chemical synthesis, experimental design, data interpretation, and general lab procedures encompassing the whole of the invention.

(2) Partial structure: (3) Physical and/or chemical properties: and (4) Functional characteristics:

Cyclic peptide and peptidyl compounds that form the core structure, to which a plurality of other functional groups are intended to modify the core structure. The compositions are know to inhibit the activity of histone deacetylase 1 and 4.

(5) Method of making the claimed invention:

Peptide synthesis (solid state and solution phase).

As stated supra, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim 1 is a broad generic, with respect to all possible compounds encompassed by the Markush of Formula I. The possible structural variations are limitless to any class of compound where the functional groups that modify the core structure are described in functional language. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. "MPEP § 2163. Here, though the claims may recite

some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification.

There are approximately 20 examples in the Tables on page 16 and 17 of the specification. While having written description for those compounds identified in those specification tables and/or examples, the specification is void of any representative peptides that embrace the whole of the Markush claimed. For example, there is insufficient description of where R_{21}-R_{23}, R_{31}-R_{33}, and R_{41}-R_{42} are independently acyclic structures with binding or cyclic structures by binding through a linear alkylene group with a one- to five-carbon main chain that would allow one of skill in the art to practice the invention as claimed. Another example in Claim 1 is "*a substituted or unsubstituted alkyl or aryl group in any structure comprising a sulfur atom capable of binding with the sulfur atom in formula (1).*" Being capable does not mean it has to, so that which is broadly claimed does not have a clear function or description. The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro inhibiting of histone deacetylase, does not reasonably provide enablement for or prevention of diseases mediated or caused by histone deacetylase, such as cancer, autoimmune disease, skin disease, or infecious disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention.

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the relative skill of those in the art; (5) the predictability or unpredictability of the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a pharmaceutical agent for treating or preventing a disease caused by histone deacetylase 1 or 4, wherein the disease caused by histone deacetylase 1 or 4 is cancer, autoimmune disease, skin disease, or infectious disease.. Thus, the claims taken together with the specification imply the administration of the instant invention would be both efficacious in treatment of those already with the claimed diseases or anyone who would take the compounds prophylactically.

(3) The state of the prior art:

Robertson KD., "DNA methylation and chromatin - unraveling the tangled web. Oncogene," 2002 Aug 12;21(35):5361-79, describes the events involving DNA methylation, histone modification, and chromatin remodeling as a "blurred image of the tangled web" implying that much is yet to be discovered and understood in how these cellular events correspond to diseases., see last paragraph of the article on page 5377.

While cancer is a target of interest in these histone deacetylase inhibiting events, the nexus between histone deacetylase as an accepted model for treating those diseases are not enabling, especially with only in vitro support in the specification. Further, the broad claims of cancer, autoimmune disease, skin disease, or infectious disease, of Claims 8 or 9 is not enabled because cancer embraces a plurality of unrelated types that do not share a common mechanism of occurrence, nor a common treatment form. Autoimmune disease reads on rheumatoid arthritis as well as HIV/AIDS to name just two, and histone deacetylase does not play a role in these diseases. Skin diseases and infectious are a braod range of diseases and most if not all do not have a nexus or connection with histone deacetylase.

(4) The relative skill of those in the art:

The relative skill of those in the art is high.

(5) The predictability or unpredictability of the art: (6) The amount of direction or guidance presented and (7) The presence or absence of working examples: (8) The quantity of experimentation necessary:

Since the connection between the inhibition of histone deacetylase to the plurality of diseases claimed remains largely unsolved, means for establishing and treating those disease through the inhibition of histone deacetylase is highly unpredictable.

The specification has provided a few in vitro assays to demonstrate enzyme inhibition, but a Petri dish or 96-well plate assay for histone deacetylase is not treatment of the particular disease claimed. It is also noted, considering the a priori unpredictability in the art with regard to treatment, that prevention of the claimed diseases is also not enabled.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The disclosed compound(s) have been shown to be useful as a in vitro inhibitor. However, the claims also encompass using the compound to prevent cancer, autoimmune disease, skin disease, or infectious disease which is clearly beyond the scope of the instantly claimed/disclosed invention. Please note that the term 'prevent' is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does “treat,” especially since it is well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regime).

Considering the state of the art as discussed by Wands Factors supra and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to test and evaluate the efficacy of the plurality of compounds claimed to the plurality of cancers, autoimmune diseases, skin diseases, or infectious diseases. It is the examiner’s position that one skilled in the art could not practice the invention commensurate in the scope of the claims without undue experimentation.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure

outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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